

PRedicting Out-of-Office Blood Pressure in the clinic (PROOF-BP): Derivation and validation of a tool to improve the accuracy of blood pressure measurement in clinical practice

Sheppard, Predicting out-of-office blood pressure

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Abstract

Patients often have lower (white coat effect) or higher (masked effect) ambulatory/home blood pressure readings compared to clinic measurements, resulting in misdiagnosis of hypertension. The present study assessed whether blood pressure and patient characteristics from a single clinic visit can accurately predict the difference between ambulatory/home and clinic blood pressure readings (the 'home-clinic difference'). A linear regression model predicting the home-clinic blood pressure difference was derived in two datasets measuring automated clinic and ambulatory/home blood pressure (n=991) using candidate predictors identified from a literature review. The model was validated in four further datasets (n=1,172) using Area Under the Receiver Operator Characteristic curve analysis. A masked effect was associated with male sex, a positive clinic blood pressure change (difference between consecutive measurements during a single visit) and a diagnosis of hypertension. Increasing age, clinic blood pressure level and pulse pressure were associated with a white coat effect. The model showed good calibration across datasets (Pearson's correlation 0.48-0.80) and performed well predicting ambulatory hypertension (AUROC 0.75, 95%CI 0.72-0.79 [systolic]; 0.87, 95%CI 0.85-0.89 [diastolic]). Used as a triaging tool for ambulatory monitoring, the model improved classification of a patient's blood pressure status compared with other guideline recommended approaches (93% [92-95%] classified correctly; US 73% [70-75%]; Canada 74% [71-77%]; UK 78% [76-81%]). This study demonstrates that patient characteristics from a single clinic visit can accurately predict a patient's ambulatory blood pressure. Utilisation of this prediction tool for triaging of ambulatory monitoring could result in more accurate diagnosis of hypertension and hence more appropriate treatment.

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Background

High blood pressure (hypertension) is an important risk factor for cardiovascular disease, a significant cause of morbidity and mortality worldwide.¹ The diagnosis and management of hypertension depends on accurate measurement of blood pressure so that antihypertensive treatment can be targeted appropriately and unnecessary adverse effects and healthcare costs can be avoided.² Traditionally, blood pressure measurement has taken place in the Primary Care Physician's office or clinic using an electronic oscillometric or aneroid sphygmomanometer (clinic blood pressure, table 1), but it has long been recognised that home or ambulatory (out-of-office) blood pressures provide more accurate estimates of a patient's true mean blood pressure.³ This is in part, because multiple readings are taken and it correlates with a range of cardiovascular outcomes and end-organ damage better than clinic blood pressure.^{4, 5}

Clinic blood pressure values are often different from out-of-office blood pressure and can lead to incorrect classification of blood pressure status and hence inappropriate management.^{6, 7} Patients with higher clinic blood pressure than the corresponding out-of-office pressure will have a negative home-clinic blood pressure difference (white coat effect) and are at risk of over-treatment (see supplemental material, figure S1).⁸ Conversely, patients with higher out-of-office blood pressures than would be expected from the corresponding clinic blood pressure have a positive home-clinic blood pressure difference (masked effect), and often remain unrecognised and therefore potentially under-treated (supplemental material, figure S1).⁹ Such patients are at increased risk of target organ damage¹⁰ and have cardiovascular morbidity and mortality not dissimilar to sustained hypertension.¹¹

Strategies to reduce these misclassifications are emerging and include the use of multiple automated clinic blood pressure readings which have been shown to reduce the white coat effect.^{12, 13} In the US, the Preventive Services Task Force¹⁴ have recently released guidelines recommending that home or ambulatory blood pressure monitoring is used to confirm a diagnosis of hypertension, an approach which has already been adopted in the UK,¹⁵ where it is considered cost-effective due to a reduction in misdiagnosis caused by the white coat effect.² However, this approach will result in some patients with sustained hypertension identified by clinic blood pressure readings being sent for arguably unnecessary out-of-office monitoring, which some patients find uncomfortable, and importantly, this strategy will not capture those patients with masked hypertension.

Recent work by some of the authors has shown that the change in clinic blood pressure over multiple automated clinic readings from a single visit can predict the home-clinic blood pressure difference.¹⁶ This study aimed to use patient characteristics and details of repeated clinic blood pressure measurements to derive a model for predicting this home-clinic blood pressure difference. Further, we aimed to validate this model and examine its application as a means to target ambulatory blood pressure monitoring more efficiently in routine clinical practice.

Methods

An extended version of the methods is available in the supplemental material. Blood pressure definitions and terminology used are summarised in table 1.

Study design and source data

The present study was an individual patient data analysis of cohort studies conducted in a Primary Care setting.^{12, 17-21} A linear regression model predicting the home-clinic blood pressure difference was derived in two datasets using candidate predictors identified from a literature review. All included studies collected relevant data including clinic, home and/or daytime ambulatory blood pressure readings using a validated electronic oscillometric blood pressure monitor and details of patient characteristics and medical history. The characteristics of patients from included studies are detailed in table 2. Individual clinic readings were available in each study permitting estimation of a variety of different definitions of clinic blood pressure. Patients in the CAMBO study¹² had their clinic blood pressure measured with a BpTRU device with either the doctor or nurse taking the first reading and then leaving the room for the remaining measurements. In all other studies, multiple clinic readings were taken in the presence of a nurse or practice reception staff.¹⁷⁻²⁰ Since our study involved secondary analysis of existing data, it was not possible to standardise protocols for blood pressure measurement across studies and specific protocols for the measurement of home and daytime ambulatory blood pressure did vary to some degree (for details see supplemental material, table S1).

Patients were selected for the derivation cohort from the BP-Eth¹⁷ and TASMINH2¹⁹ studies (n=991) because these were considered to be sufficiently large and representative of the population likely to undergo blood pressure monitoring for diagnosis and management of hypertension. Patients from the remaining four studies^{12, 18, 20, 21} were utilised in the validation cohort (n=1,172).

Statistical Analysis

Selection of candidate predictors

Candidate predictors considered for inclusion in the model were identified by literature review.²² Of the 60 identified, a total of 14 variables were considered for inclusion in the model, including age, sex, body mass index, diagnosis of hypertension and time since diagnosis, antihypertensive prescription, smoking status, alcohol consumption, diagnosis of cardiovascular disease, clinic blood pressure level (systolic/diastolic) and multiple clinic blood pressure characteristics defined as previously described.¹⁶ These characteristics were the difference between the first and last clinic blood pressure reading (referred to as the ‘clinic blood pressure change’ [estimated from 3 or 6 readings]), the rate of the change in clinic blood pressure (referred to as the ‘blood pressure slope’ [estimated from 3 or 6 readings]) and the ‘curvature’ of this change in clinic blood pressure (referred to as the ‘blood pressure quadratic’ [estimated from 6 readings]). Age, sex and clinic blood pressure variables were included in the final model *a priori* because they were cited as significant predictors of white coat or masked hypertension in more than twice as many published studies compared to other predictors in a previous literature review.^{22, 23} Backwards stepwise selection was used to select the remaining candidate predictors for the final model. Only predictors reaching a significance level of $p < 0.05$ were included.

Model derivation

A complete case analysis was conducted due to low amounts of missing data. Two separate linear regression models were constructed examining factors that predict the systolic and diastolic home-clinic blood pressure difference (1st clinic blood pressure reading minus mean out-of-office blood pressure). Out-of-office blood pressure was taken to be mean daytime ambulatory blood pressure where available, otherwise mean home blood pressure was used (table 1).^{19, 20} Due to co-linearity between some of the candidate predictors listed above, separate models were compared in three stages using likelihood ratio tests. The best fitting

model at each stage was considered in the next stage and where there was no significant difference in model fit, the most parsimonious model was selected. Stage one compared five different prediction models examining combinations of clinic blood pressure characteristic. Stage two compared the best fitting model from the first step using different definitions of clinic blood pressure (1st clinic reading; mean of 1-3 readings; mean of 2-3 readings; mean of 1-6 readings; or the mean of 2-6 readings). The final stage explored pre-specified interactions of all candidate predictors with age, sex and diagnosis of hypertension and the interaction between clinic blood pressure and the characteristics of the change in clinic blood pressure. Ninety-five percent confidence intervals (CIs) for model coefficients were estimated with bootstrap resampling (200 replications). Model coefficients are presented for centred continuous variables in the final model.

Model validation and performance

The agreement between predicted and actual home-clinic blood pressure differences was examined in both derivation and validation cohorts using Pearson's correlation coefficient and Bland-Altman plots. A 'model-adjusted' clinic blood pressure value was calculated by combining the original clinic pressure (1st clinic reading) with the home-clinic blood pressure difference estimated from the model. The ability of the 'model-adjusted' clinic blood pressure to predict out-of-office hypertension was assessed using Area Under the Receiver Operator Characteristic (AUROC) curve statistics. High AUROC values (up to 1) indicate better model discrimination.

Potential strategies for referral for out-of-office monitoring were explored in the derivation cohort (supplemental material, tables S2 and S3), with the optimal strategy defined as a threshold which produced an overall classification error of $\leq 10\%$ with the lowest proportion

of patients referred for out-of-office monitoring. Model performance detecting true out-of-office hypertension was compared to existing strategies for blood pressure measurement described in international hypertension guidelines (supplemental material, table S4).^{15, 24-26} The model was also applied to a nominal population from our validation cohort, with a comparable distribution of clinic blood pressures to that documented in the Health Survey for England. Using this nominal population, the number of patients being correctly diagnosed with hypertension per 1,000 individuals was compared to the current NICE diagnostic algorithm¹⁵ (considered best of the rest).

Sensitivity analyses explored the model performance by individual study, predicting home or daytime ambulatory blood pressure, in patients with raised clinic blood pressure and those with controlled or normal clinic blood pressure. Were also examined a revised diagnostic strategy which does not utilise the PROOF-BP algorithm, but in which patients with a clinic blood pressure between 130/85mmHg and 160/100mmHg were referred for out-of-office monitoring. All sensitivity analyses were conducted in the validation cohort (except those by individual study which compared all available data).

All analyses were performed in STATA version 13.1 (MP parallel edition, StataCorp, Texas, USA). Data are presented as proportions of the total study population or means with standard deviation or 95% CIs unless otherwise stated. Ethical approval was given for all individual studies contributing data but approval for secondary analysis using anonymised data was not required.

Results

Characteristics of the study cohort

Of the 2,470 patients with out-of-office blood pressure measurements enrolled across the six studies, relevant data were available for analysis in a total of 2,163 patients (991 patients in the derivation cohort; 1,172 patients in the validation cohort). Relevant data were not available in some patients enrolled in the CAMBO study¹² because not all centres recorded the individual automated clinic blood pressure readings required for this analysis (table 2, table S1). Characteristics of the derivation and validation cohorts were similar in terms of age, sex, the prevalence of systolic white coat hypertension and systolic masked hypertension (see supplemental material, table S5).

Model derivation

Goodness-of-fit was similar between models examining three or six clinic blood pressure readings (derivation stage 1; adjusted R^2 0.50-0.52) and those using different definitions of clinic blood pressure (derivation stage 2; adjusted R^2 0.50-0.52). The most parsimonious model selected at each stage was that which utilised patient characteristics along with the clinic blood pressure change (estimated from three clinic readings), with the 1st clinic reading as an estimate of clinic blood pressure.

The systolic masked effect (a positive home-clinic difference) was associated with male sex, a positive clinic blood pressure change and a previous diagnosis of hypertension (figure 1). The same factors were predictive of a diastolic masked effect with the exception of male sex. The systolic white coat effect (negative home-clinic blood pressure difference) was associated with increasing clinic blood pressure only (figure 1). The diastolic white coat effect was associated with increasing clinic blood pressure, increasing age and increasing pulse pressure. The final model included significant interactions between age, sex, clinic

blood pressure, the clinic blood pressure change, pulse pressure, BMI, history of cardiovascular disease, presence of an antihypertensive prescription, history of hypertension and duration of hypertension. The final model (centred) coefficients are presented in table 3 and the full equation is given in the supplemental material (figure S6).

Model validation and performance

The final model showed good calibration across all derivation and validation datasets (Pearson's correlation 0.62-0.80 [systolic]; 0.48-0.80 [diastolic]; $p < 0.001$) (supplemental material, figures S2 and S3). At the extremes of home-clinic blood pressure difference the model was less accurate, as evidenced by the slight skew observed in the Bland-Altman plots (supplemental material, figures S4 and S5), suggesting the model under-predicts those with a large masked effect and over-predicts those with a large white coat effect.

The model was good at discriminating out-of-office hypertension (masked or sustained hypertension) in the derivation cohort (AUROC 0.80, 95% CI 0.78-0.83 [systolic model]; 0.82, 95% CI 0.80-0.85 [diastolic model]) and this discrimination was maintained in the validation cohort (AUROC 0.75, 95% CI 0.72-0.79 [systolic model]; 0.87, 95% CI 0.85-0.89 [diastolic model]) (figure 2). Using the 'model-adjusted' clinic blood pressure, the optimal thresholds for referral for out-of-office monitoring were $\geq 130/80$ mmHg and $< 145/90$ mmHg. In other words, below a 'model-adjusted' blood pressure of 130/80mmHg, patients were confidently predicted as normotensive and those with a 'model-adjusted' blood pressure of 145/90mmHg or greater were considered hypertensive. Anyone with a 'model-adjusted' blood pressure between the two required out-of-office measurements. Using this model-adjusted blood pressure to triage patients for out-of-office monitoring, 93% of cases were correctly classified. This was an improvement of up to 29% compared to strategies

recommended in current clinical guidelines (PROOF-BP 93% [92-95%]; AHA 73% [70-75%]; CHEP 74% [71-77%]; ESH 73% [70-75%]; NICE 78% [76-81%]) with similar utilisation of out-of-office monitoring (PROOF-BP, 58% referred [55-61%]; vs. NICE, 54% referred, [51-57%]) (table 4). In a nominal representative population, for every 1,000 people aged 45-74 years screened with the new algorithm, correct classification would be gained for 910 patients with 395 diagnosed as hypertensive, compared with the next best strategy (NICE algorithm) where 853 would be correctly classified and only 274 diagnosed as hypertensive. The additional 121 diagnoses of hypertension result from the detection of those patients with masked hypertension.

Sensitivity analyses

The results of the sensitivity analyses are detailed in the online appendix (supplemental material, table S6). Model performance was consistent across individual studies (AUROC 0.61-0.78 [systolic model]; 0.74-0.91 [diastolic model]) and the new algorithm resulted in better targeting of out-of-office blood pressure compared to a revised diagnostic strategy using clinic blood pressure alone to triage patients for out-of-office monitoring. Using the new algorithm to triage only those patients with raised clinic blood pressure (*i.e.* only considering those patients with a potential white coat effect) resulted in correct classification of 94% of patients with only 45% requiring out-of-office monitoring (see supplemental material, table S6).

Discussion

This study describes a clinical prediction model which combines patient characteristics (age, sex, BMI, history of hypertension, cardiovascular disease and antihypertensive treatment) and three clinic blood pressure measurements from a single visit to accurately predict a patient's

out-of-office blood pressure. Used as a triaging tool for out-of-office monitoring, detection of hypertension or uncontrolled blood pressure was markedly improved from existing diagnostic and management strategies, specifically including those with hitherto unrecognised masked hypertension.

Strengths and limitations

This retrospective study utilised a large cohort of patients from six previous studies providing a population representative of patients across the UK and North America undergoing blood pressure measurement in Primary Care. Sensitivity analyses revealed consistent model performance across individual studies, suggesting that it would be effective regardless of the electronic blood pressure monitoring device (BpTRU, Stabil-O-Graph) or measurement protocol used (rest period vs. no rest period; nurse present during measurement vs. nurse not present; automatic readings vs. patient/nurse initiated readings; 1 minute vs. 2 minute intervals between readings). It is well known that blood pressure measurements made under controlled conditions in a research setting are not necessarily comparable to those made by a physician in routine clinical practice.^{24, 27, 28} Differences occur for a variety of reasons, including the use of inadequate or uncalibrated devices²⁹⁻³¹ and suboptimal measurement techniques.³²⁻³⁴ Indeed, the present algorithm requires three consecutive blood pressure readings to be taken at a single clinic visit and whilst this is recommended in most hypertension guidelines,^{15, 24-26} ensuring this approach is adhered to in routine practice may require some education of physicians and nurses. Therefore, although this prediction model is shown to be accurate in a research setting, is not guaranteed to work in routine clinical practice and prospective validation of the PROOF-BP prediction tool in a clinical setting warrants further investigation.

Bland-Altman plots demonstrated that the PROOF-BP prediction model tends to underestimate those with a large masked effect and overestimate those with a large white coat effect. This is likely to be explained by the underlying population in the derivation cohort which contained a higher proportion of hypertensive (defined by clinic readings) patients on treatment (704 [71%]), a population known to have an exaggerated white coat effect compared to normotensives (supplemental material, figure S1).³⁵ Whilst the model was less accurate at extremes of home-clinic blood pressure difference, it showed good performance detecting out-of-office hypertension around the clinical threshold (140/90mmHg) where the average home-clinic blood pressure difference is smaller.³⁵

The present analyses used home blood pressure data to define out-of-office blood pressure where daytime ambulatory measurements were not available (table 1). Some argue that 24-hour ambulatory blood pressure should be used as the ‘gold standard’ measure of blood pressure,²⁶ because it contains information about night-time blood pressure which includes additional prognostic information. However, the recent review by the US Preventive Services Task Force found no apparent difference among 24-hour, daytime, and night-time ambulatory blood pressure measurement protocols for prediction of cardiovascular outcomes¹⁴ and a sensitivity analysis in the present study demonstrated no change in the accuracy of the PROOF-BP prediction model using home or daytime ambulatory readings.

Comparison with previous literature

Many studies have examined the association between patient characteristics and the home-clinic blood pressure difference, noting age,³⁶⁻³⁸ sex³⁶⁻³⁹ and clinic blood pressure level,³⁶⁻³⁹ along with anxiety,^{40, 41} stress⁴² and other factors²² as significant independent predictors of white coat or masked hypertension. The findings of the present study were consistent with

previous literature, showing age, sex, clinic blood pressure, pulse pressure and a history of hypertension as significant predictors of the home-clinic blood pressure difference.

Interestingly, female sex was not a significant predictor of the white coat effect, although it was included *a priori* in the final prediction model since this association has been well defined in the previous literature.^{36, 38}

Few studies have suggested a strategy for targeted use of out-of-office blood pressure in routine clinical practice. Myers⁴³ and Godwin *et al.*,⁴⁴ have proposed the use of multiple (automated) office blood pressure readings taken using the BpTRU device to identify patients high normal blood pressure (130/80mmHg to 139/89mmHg) who could be referred for ambulatory blood pressure to confirm the presence of masked hypertension. Similarly, Viera *et al.*,⁴⁵ examined optimal automated clinic blood pressure levels for referral for out-of-office monitoring in patients with normal clinic pressure for detection of masked hypertension. However, they concluded that using clinic blood pressure alone was not sufficient, because of high referral rates, and suggested that a combination of factors, including patient characteristics might be more effective at targeting out-of-office blood pressure more efficiently.

Implications for clinical practice

The US Preventive Services Task Force¹⁴ recently released guidelines recommending that ambulatory blood pressure monitoring is used to confirm a diagnosis of hypertension. It is anticipated that these guidelines will follow a similar approach to that advocated in the UK by NICE, which does not capture those patients with masked hypertension. The present analyses propose a method for capturing nearly all patients with truly raised out-of-office blood pressure which is likely to result in a small increase in the amount of out-of-office

monitoring required in routine practice but could still be very cost-effective if it reduces the current best practice involving indiscriminate application of ambulatory monitoring.^{2, 14, 15}

Indeed, our sensitivity analyses show that in patients with raised clinic readings, the PROOF-BP prediction model could potentially reduce the proportion of referrals for daytime ambulatory monitoring by over half to 285/629 (45%), with nearly all patients being accurately diagnosed (589/629 [94%] correctly classified) and acceptable false positive and false negative rates (6% and 0% respectively). Importantly, this new method identifies patients with possible masked hypertension which is otherwise unsuspected unless there is evidence of unexpected end organ damage.

An algorithm for using the PROOF-BP prediction tool in routine clinical practice is presented in figure 3. Electronic blood pressure monitors which take up to three consecutive readings (at 1 minute intervals) are now cheap and routinely available, permitting utilisation of this algorithm before, during or after a standard physician consultation in Primary Care. The prediction model could easily be incorporated into general practice computer systems, accessed as an online calculator or even built into smartphones linked to blood pressure monitors to facilitate implementation in routine clinical practice. This novel approach to measurement and management would require ‘buy in’ from both patients and practitioners and therefore some degree of education may be required during implementation.

Perspectives

The present study shows that a combination of simple patient characteristics with three clinic blood pressure measurements from a single visit can accurately identify those patients requiring out-of-office blood pressure monitoring for suspected white coat and arguably most importantly masked hypertension. This prediction model has the potential improve the

accuracy of diagnosis and management of hypertension in Primary Care and prospective validation in routine clinical practice along with analysis of cost-effectiveness are now warranted.

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Declaration of competing interests: RJMcM has received equipment for research purposes from Omron and Lloyds Healthcare. CH has received expenses and payments for his media work from Channel 4, BBC, FreshOne TV productions and the Guardian, and also expenses from the WHO and the US FDA. He is also an expert witness in an ongoing medical device legal case, has received payment from BUPA for analyzing and appraising guidelines and

income from the publication of a series of toolkit books published by Blackwells. FDRH has received limited research support in terms of blood pressure devices from Microlife and BpTRU. BW works in academic collaboration with Healthstats, Singapore, in developing novel blood pressure monitoring approaches. All other authors report no other relevant conflicts of interest.

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Novelty and Significance

What Is New?

- This study shows a simple linear regression model incorporating patient characteristics and three consecutive clinic blood pressure measurements from a single clinic visit can accurately identify those patients requiring out-of-office blood pressure monitoring for suspected white coat or masked hypertension.
- The model performance was consistent across populations, and studies using different blood pressure monitors and measurement techniques, suggesting the results are widely applicable across Primary Care.

What Is Relevant?

- This prediction model could be used as an online calculator or integrated into practice computer systems for triaging of out-of-office monitoring to permit detection of those patients with white coat or masked hypertension in routine clinical practice.
- The present analyses suggest such an approach would improve the detection of hypertension and provide a strategy for capturing patients with apparent masked hypertension for the first time.

Summary

Our findings suggest that it is possible to predict which patients are most likely to display a white coat or masked effect, using patient characteristics and multiple clinic blood pressure measurements from a single clinic visit.

Figure legends

Figure 1. Coefficient plot showing predictors of the systolic and diastolic home-clinic blood pressure difference

Panel A = Continuous predictors; **Panel B** = Binary predictors; BP=blood pressure; BMI=body mass index; CVD=cardiovascular disease.

All coefficients are presented from the model prior to stepwise selection.

Coefficients for continuous variables are presented as centred values per unit increase.

Figure 2. Area under the receiver operator characteristic curve analysis showing performance of systolic/diastolic blood pressure prediction models for discrimination of out-of-office hypertension

Panel A = systolic blood pressure (sBP) prediction model; **Panel B** = diastolic blood pressure (dBP) prediction model; AUROC = Area Under the Receiver Operator Characteristic curve.

Figure 3. Algorithm for using the PROOF-BP prediction model to triage patients for out-of-office blood pressure monitoring

BP= Blood pressure; PROOF-BP=PRedicting Out-of-OFFice Blood Pressure in clinic tool; Existing strategies are based on the hypertension diagnostic pathway specified by the US Preventive Services Task Force and the National Institute for Health and Care Excellence.

Tables

Table 1. Definitions of blood pressure measurements described in the present study

Term	Definition
Clinic blood pressure	1 st clinic blood pressure reading from a single clinic visit using an electronic oscillometric sphygmomanometer
Multiple clinic blood pressure readings	3-6 clinic blood pressure readings from a single clinic visit using an automated oscillometric sphygmomanometer
Clinic blood pressure change	Difference between the 1 st and 3 rd (or 6 th) clinic blood pressure reading taken in a single clinic visit using an automated oscillometric sphygmomanometer
Daytime ambulatory blood pressure	Ambulatory blood pressure measured at 15-60 minute intervals during the daytime (definition of daytime and interval varies between studies)
Home blood pressure	Mean of 6 days of readings (2 readings per day taken in the morning) after discarding the 1st days' readings
Out-of-office blood pressure	Daytime ambulatory blood pressure or home blood pressure (if daytime ambulatory blood pressure is not available)
Out-of-office hypertension	Daytime ambulatory blood pressure or home blood pressure $\geq 135/85$ mmHg
Home-clinic blood pressure difference	The difference between out-of-office blood pressure and automated blood pressure measured in the clinic
'Model-adjusted' clinic blood pressure	1 st clinic blood pressure reading added to the predicted home-clinic blood pressure difference (estimated by the PROOF-BP prediction algorithm).

PROOF-BP = PRedicting Out-of-OFFice Blood Pressure in the clinic

Table 2. Characteristics of studies used for model derivation and validation

Study	Author (year)	Total population	Used in analysis	Age (mean±SD)	Sex (% male)	Population	CHD	Stroke	Diabetes	Hypertensive ^a	Years with high BP (mean±SD)	Treatment for hypertension	White coat Hypertension ^b	Masked Hypertension ^b
BP-Eth^c	Martin <i>et al.</i> , (2014) ¹⁷	771	771	59±10	375 (49%)	Unselected	81 (11%)	33 (4%)	130 (17%)	344 (45%)	10±8	484 (63%)	83 (11%)	136 (19%)
CAMBO	Myers <i>et al.</i> , (2011) ¹²	555	379 ^d	64±10	131 (35%)	Isolated systolic hypertensives	0 (0%)	0 (0%)	0 (0%)	166 (44%)	9±9	364 (96%)	52 (16%)	64 (19%)
HITS	Mckinstry <i>et al.</i> , (2013) ¹⁸	401	401	61±11	237 (59%)	Uncontrolled hypertensives	n/a	0 (0%)	0 (0%)	379 (95%)	n/a	352 (88%)	23 (6%)	42 (10%)
Oxford self-monitoring study	Nunan <i>et al.</i> , (2015) ²¹	203	203	56±10	107 (53%)	Untreated, clinic BP ≥130/80mmHg	0 (0%)	0 (0%)	11 (5%)	109 (54%)	0±0	0 (0%)	67 (33%)	13 (6%)
TASMINH2^c	McManus <i>et al.</i> , (2010) ¹⁹	527	220 ^e	67±9	103 (47%)	Uncontrolled hypertensives	20 (9%)	12 (5%)	18 (8%)	172 (78%)	10±8	220 (100%)	42 (21%)	11 (5%)
TASMINH-SR	McManus <i>et al.</i> , (2014) ²⁰	552	189 ^e	69±9	115 (61%)	Uncontrolled, high risk hypertensives	58 (31%)	30 (16%)	81 (43%)	134 (71%)	11±9	160 (85%)	18 (10%)	53 (29%)

^aHypertensive according to home or ambulatory blood pressure monitoring^bDefined according to systolic blood pressure^cStudies utilised for model derivation

^dPatients in the control arm (multiple clinic BP readings not taken); those recruited from centres where complete clinic BP readings were not documented

^ePatients in the control arm of the trial and those with missing home BP data

CHD = Coronary heart disease; BP = blood pressure; SD = Standard deviation

Hypertension defined as daytime out-of-office blood pressure (home or ambulatory monitoring) of $\geq 135/85$ mmHg. White coat systolic hypertension defined as a clinic blood pressure ≥ 140 mmHg (mean of 2nd & 3rd readings) but an out-of-office blood pressure of < 135 mmHg. Masked systolic hypertension defined as a clinic blood pressure (mean of 2nd & 3rd readings) < 140 mmHg but an out-of-office blood pressure of ≥ 135 mmHg. All percentages are given as a proportion of those patients with available data.

Table 3. Linear regression model for prediction of the systolic/diastolic home-clinic blood pressure difference

Model term	Prediction model with interaction terms					
	Systolic prediction model			Diastolic prediction model		
	β	95% CI	<i>p</i> value	β	95% CI	<i>p</i> value
Age (years)	0.07	-0.02 to 0.17	0.134	-0.33	-0.62 to -0.05	0.022
Sex (male)	3.41	0.23 to 6.60	0.036	3.33	1.78 to 4.87	<0.001
Clinic blood pressure (1 st reading; mmHg)	-0.50	-0.58 to -0.43	<0.001	-0.47	-0.51 to -0.42	<0.001
Clinic blood pressure change (readings 1-3; mmHg)	0.36	0.26 to 0.46	<0.001	0.31	0.21 to 0.42	<0.001
Body mass index (kg/m ²)	-0.21	-0.37 to -0.04	0.012	-0.07	-0.16 to 0.01	0.096
Previous diagnosis of hypertension (yes)	-5.07	-12.15 to 2.01	0.161	-0.03	-3.55 to 3.49	0.987
Time since diagnosis of hypertension (years)	0.18	0.00 to 0.35	0.053			
Antihypertensive prescription (yes)	6.94	0.42 to 13.46	0.037	2.37	-1.30 to 6.04	0.206
History of cardiovascular disease (yes)				-0.40	-1.69 to 0.89	0.543
Pulse pressure (1 st reading; mmHg)	-0.04	-0.13 to 0.05	0.397	-0.06	-0.09 to -0.03	<0.001
Age \times clinic blood pressure	-0.01	-0.01 to -0.00	0.027			
Age \times pulse pressure	0.01	0.00 to 0.02	0.030			
Age \times clinic blood pressure change				0.01	0.00 to 0.02	0.014
Age \times body mass index				0.01	0.00 to 0.02	0.039
Age \times history of cardiovascular disease				0.18	0.02 to 0.33	0.023
Age \times antihypertensive prescription at baseline				-0.13	-0.24 to -0.03	0.010
Sex \times body mass index	0.30	0.01 to 0.58	0.041			
Sex \times time since diagnosis of hypertension	-0.26	-0.50 to -0.02	0.034			
Sex \times antihypertensive prescription at baseline	-14.74	-23.33 to -6.15	0.001	-8.00	-12.45 to -3.54	<0.001
Sex \times previous diagnosis of hypertension	13.39	4.57 to 22.21	0.003	4.63	0.40 to 8.85	0.033
Constant	-9.09	-11.55 to -6.64	<0.001	-6.98	-8.24 to -5.72	<0.001

CI = confidence intervals. β coefficients and 95% confidence intervals given in mmHg. β coefficients for continuous variables are presented as centred values per unit increase unless otherwise stated.

Table 4. Comparison of model performance with current clinical practice in the validation cohort (n=1,100)

Guideline (year)	Systolic AUC (95% CI)	Diastolic AUC (95% CI)	Hypertensive (True positive)	Normotensive (True negative)	White coat hypertensive (False positive)	Masked hypertensive (False negative)	Correctly classified	Referral for ABPM
AHA (2005)²⁴	0.74 (0.71-0.77)	0.85 (0.83-0.87)	625 (57%)	173 (16%)	178 (16%)	124 (11%)	798 (73%)	0 (0%)
CHEP (2014)²⁵	0.76 (0.73-0.79)	0.87 (0.85-0.89)	642 (58%)	172 (16%)	179 (16%)	107 (10%)	814 (74%)	0 (0%)
ESH (2013)^{26a}	0.74 (0.71-0.77)	0.86 (0.84-0.88)	596 (54%)	203 (18%)	148 (13%)	151 (14%)	799 (73%)	0 (0%)
NICE (2011)¹⁵	0.73 (0.70-0.76)	0.84 (0.82-0.87)	513 (47%)	349 (32%)	2 (0.2%)	236 (21%)	862 (78%)	590 (54%)
PROOF-BP (2016)	0.75 (0.72-0.78)	0.87 (0.85-0.89)	720 (65%)	306 (28%)	45 (4%)	29 (3%)	1,026 (93%)	640 (58%)

Data from HITS,¹⁸ TASMINH-SR,²⁰ CAMBO¹² and Oxford self-monitoring studies²¹

AUC=Area Under the receiver operator characteristic Curve; CI=Confidence Intervals; ABPM=Ambulatory blood pressure monitoring;

AHA=American Heart Association; CHEP=Canadian Hypertension Education Programme; European Society of Hypertension; NICE=National Institute for health and Care Excellence; PROOF-BP=PRedicting Out-of-Office Blood Pressure in clinic tool.

^aAnalysis only conducted in 1,098 patients due to missing data.